Proposed Registration Decision PRD2012-14

Natamycin

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

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Overview

Proposed Registration Decision for Natamycin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Natamycin TGAI and Zivion M containing the technical grade active ingredient natamycin, to suppress dry bubble disease in mushroom production.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Natamycin TGAI and Zivion M.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on natamycin, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on natamycin, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Natamycin?

Natamycin is a substance naturally produced by the soil bacterium *Streptomyces natalensis* that inactivates germinating fungal spores.

Health Considerations

Can Approved Uses of Natamycin Affect Human Health?

Natamycin is unlikely to affect human health when it is used according to label directions.

Exposure to natamycin may occur when handling the end-use product, Zivion M, which is a fungicide to suppress dry bubble disease on button mushrooms (*Agaricus bisporus*). When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

The technical grade active ingredient, natamycin (98%), is of low acute toxicity via the oral, dermal, and inhalation routes. It is severely irritating to the eyes and slightly irritating to the skin. Natamycin is not considered a dermal sensitizer. Cautionary statements indicating the potential for eye irritation are required on the technical grade active ingredient product label.

Dermal exposure is possible for workers handling the end-use product, Zivion M, and for workers engaged in post-application activities such as harvesting, clean-up and maintenance. Therefore, precautionary measures including personal protective equipment (PPE) are required on the end-use product label to mitigate such exposure concerns. The potential for bystander exposure is expected to be minimal as non-workers are not expected to be present in the enclosed mushroom growing houses during the applications.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Natamycin has a long history of use as a food additive to prevent spoilage by molds and yeasts, and is approved as a direct food additive in more than 70 countries. The end-use product, Zivion M, will be applied directly to the mushroom bed at casing and at pinning; however, food residue exposure is not expected to be of concern as conservative exposure estimates indicate that the proposed use of Zivion M will not appreciably increase the dietary exposure to natamycin above what is currently expected from its use as a food additive.

Therefore, the proposed use of Zivion M is not expected to result in unacceptable dietary risks when the product is used according to label instructions. In addition, as Zivion M is to be applied inside an enclosed growing house, exposure to natamycin in drinking water is not expected to occur. The PMRA has also determined that a maximum residue limit (MRL) is not required for natamycin.

Occupational Risks From Handling Zivion M

Occupational risks are not of concern when Zivion M is used according to label directions, which include protective measures.

Occupational exposure to individuals handling Zivion M is not expected to result in unacceptable risk when the proposed product is used according to label directions.

Precautionary and hygiene statements on the label (for example, wearing of PPE) are considered adequate to protect individuals from potential risks from occupational exposure.

Environmental Considerations

What Happens When Natamycin Is Introduced Into the Environment?

The proposed use of natamycin in mushroom houses is not expected to result in environmental exposure.

Natamycin is a naturally occurring substance. When used as proposed in mushroom houses, negligible amounts of natamycin are expected to enter the environment either during use or through the disposal of spent compost medium.

Value Considerations

What Is the Value of Zivion M?

Zivion M is a bio-fungicide that suppresses dry bubble disease in mushroom production.

Zivion M reduces the development of dry bubble disease in commercial mushrooms. It does not affect mycelial growth, and so does not negatively affect mushroom yield.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Natamycin TGAI and Zivion M to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

The signal words 'DANGER – EYE IRRITANT' are required on the principal display panel of the Natamycin TGAI label. The statements 'Severely irritating to the eye, DO NOT get in eyes' are required on the secondary display panel of the Natamycin TGAI label.

The personal protective equipment for all handling, clean-up and maintenance activities required on the Zivion M label includes a long sleeved shirt, long pants, shoes and socks, waterproof gloves, and safety glasses.

Environment

No mitigative measures are required for the proposed use of Natamycin TGAI and its end-use product, Zivion M, in mushroom growing facilities.

Next Steps

Before making a final registration decision on natamycin, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

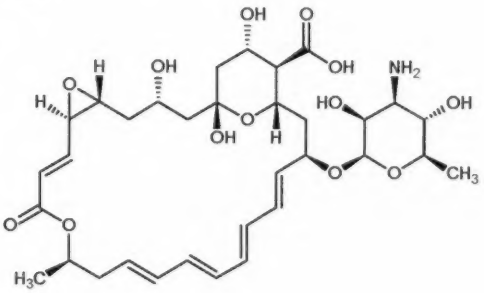
When the PMRA makes its registration decision, it will publish a Registration Decision on natamycin (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Natamycin

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Natamycin
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*(1R,3S,5R,7R,8E,12R,14E,16E,18E,20E,22R,24S,25R,26S)*-22-[(3-Amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,26-trihydroxy-12-methyl-10-oxo-6,11,28-trioxatricyclo[22.3.1.$0^{5,7}$]octacosa-8,14,16,18,20-pentaene-25-carboxylic acid
2. Chemical Abstracts Service (CAS)	6,11,28-Trioxatricyclo[22.3.1.$0^{5,7}$]octacosa-8,14,16,18,20-pentaene-25-carboxylic acid,22-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,26-trihydroxy-12-methyl-10-oxo-, *(1R,3S,5R,7R,8E,12R,14E,16E,18E,20E,22R,24S,25R,26S)*-
CAS number	7681-93-8
Molecular formula	$C_{33}H_{47}NO_{13}$
Molecular weight	665.7
Structural formula	
Purity of the active ingredient	91.02%

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—Natamycin TGAI

Property	Result
Colour and physical state	White to pale cream powder or flat crystals
Odour	Odourless to lightly acidulous.
Melting range	Does not melt; darkens at 200°C; vigorously decomposes at 280-300°C.
Boiling point or range	Not applicable, the product is a solid at room temperature.
Density	Loose bulk density 0.3 g/mL Tapped bulk density 0.59 g/mL
Vapour pressure at 20°C	Not applicable, the product is a solid.
Henry's law constant at 20°C	2.27×10^{-26} Pa·m^3·mole^{-1}
Ultraviolet (UV)-visible spectrum	Absorption maxima at 292, 305 and 320 nm. No absorption maxima above 350 nm.
Solubility in water at 20°C	30-50 ppm @ 20-25°C and pH 5- 7.5; very soluble at pH $\geq$ 10 or pH $\leq$ 2, but rapidly degrades
Solubility in organic solvents at 20°C	Methanol = 0.3%; Ethanol = 40 ppm; Acetone = 10 ppm; Ethyl acetate = 10 ppm; Glacial acetic acid = 25%
n-Octanol-water partition coefficient (K_{ow})	Log K_{ow} = –3.67
Dissociation constant (pK_a)	Isoelectric point pH 6.5; pKa 8.35 and 4.6
Stability (temperature, metal)	Natamycin was found stable at 54°C for 14 days. Storage stability studies supporting pharmaceutical uses found acceptable stability in tests of 2 to 5 years in duration. Natamycin is degraded by contact with most metals and metal ions. However, the product is not packaged in metal containers.

End-Use Product—Zivion M

Property	Result
Colour	Colourless
Odour	Odourless
Physical state	Viscous liquid
Formulation type	Suspension (SU)
Guarantee	10.34%
Container material and description	HDPE plastic bucket, jerry can, drum or jumbo container (5 to 1000 Litres)
Density	1.08 g/mL
pH of 1% dispersion in water	6.5 (1% aqueous solution). May vary between 5 to 7.5
Oxidizing or reducing action	Not applicable. Does not contain oxidizing or reducing components.
Storage stability	The product is stable when stored for 12 and 18 months in HDPE plastic bottles at 25°C.
Corrosion characteristics	The product is not corrosive.

Property	Result
Explodability	Not applicable. The product does not contain any substance capable of exploding.

1.3 Directions for Use

Zivion M is to be applied once at casing and once at pinning. Apply 2.0 mL of Zivion M per square metre diluted in sufficient water to ensure an even application.

1.4 Mode of Action

Natamycin inactivates germinating fungal spores, but does not kill them. This active ingredient binds to ergosterol in fungal cell walls and inhibits growth. Natamycin has historically been used as a food preservative and has no activity against growing mycelium or bacteria.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Natamycin TGAI have been validated and assessed to be acceptable.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for natamycin consisting of toxicity studies and waiver rationales was conducted. The scientific quality of the data is acceptable and the database is sufficiently complete to define the majority of the toxic effects that may result from exposure resulting from the use of this pest control product.

The applicant submitted acute toxicity (oral, dermal and inhalation), irritation (ocular and dermal), sensitization, short-term toxicity, and mutagenicity studies on natamycin. Natamycin (98%) was of low acute toxicity via the oral, dermal, and inhalation routes (Table 1, Appendix I). It was severely irritating to the eyes, slightly irritating to the skin, and was not a dermal sensitizer. Natamycin was considered to be non-mutagenic in a bacterial reverse mutation assay and in an *in vitro* mammalian chromosomal aberration assay.

A data waiver rationale was submitted requesting that the acute toxicity, irritation and sensitization studies submitted in support of Natamycin TGAI be used to fulfill the toxicology data requirements for Zivion M, with the exception of primary eye irritation for which data was submitted. This data waiver rationale was accepted. The primary eye irritation study submitted for Zivion M categorizes it as non to minimally irritating to the eyes.

A 90-day oral toxicity study in rats was provided for natamycin. The lowest adverse effect level (LOAEL) of the study was determined to be 2000 ppm in the diet, the highest dose tested (204 mg/kg bw/day for males, 238 mg/kg bw/day for females,) based on significantly lower body weight. The no observed adverse effect level (NOAEL) was determined to be 500 ppm in the diet (42 mg/kg bw/day for males, 48 mg/kg bw/day for females).

A data waiver rationale was considered to be acceptable to address the prenatal developmental toxicity of natamycin, based mainly on a comprehensive review of natamycin by the European Food Safety Authority (EFSA, 2009) and its associated references, which in turn relied on the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1968, 1976, and 2002) reviews on natamycin (aka pimaricin). The EFSA/JECFA reviews examined three subchronic toxicity studies (two in rat, one in dog), two 2-year chronic studies (rat, dog), a three-generation reproductive toxicity study (rat), and a three-generation developmental toxicity study (rat). Based on the weight of evidence, the NOAEL for reproductive and developmental toxicity is 50 mg/kg bw/day.

3.2 Food Residue Exposure Assessment

3.2.1 Food and Drinking Water

A residue study was conducted to determine the residues of natamycin on white button mushrooms and the growth substrate following two to four treatments with a product containing 10% w/w natamycin. The study was performed at the maximum label application rate of 2 mL/m^2, and treatments occurred at casing, pinning, between the first and second breaks, and between the second and third breaks, depending on the treatment group (two, three or four applications). Each treatment was replicated four times with negative and positive controls. Maximum residue levels in mushrooms receiving two, three, or four applications of test material were 0.0890 mg/kg, 0.2370 mg/kg, and 0.1452 mg/kg, respectively. Washing the mushrooms under a gentle stream of water greatly reduced the residues of natamycin (maximum residue after three applications of test substance and after washing with water was 0.0755 mg/kg; maximum residue at four applications after washing was 0.0220 mg/kg). Natamycin residues were not detected in the compost or casing samples after steam sterilization.

This residue data, along with consumption data based on per capita intake of farm and retail mushrooms, was used to conservatively estimate exposure to natamycin from consumption of treated mushrooms, assuming mushrooms were left unwashed. Dietary exposure to natamycin from consumption of unwashed mushrooms is estimated to be 0.0107 mg a.i./kg bw/year, or 0.00003 mg a.i./kg bw/day.

Food residue exposure to natamycin from consumption of treated mushrooms is not expected to be of concern as conservative exposure estimates show that it will not appreciably increase the dietary exposure to natamycin to levels above what is currently expected from its use as a food additive. The maximum levels detected in the provided residue study are much lower than the levels established in the Food and Drug Regulations for use on cheese (up to 20 ppm), and the levels proposed in the Codex draft General Standard for Food Additives for cheese (40 mg/kg) and meat (up to 20 mg/kg). Results from the residue study also showed that residues diminished greatly after washing the mushrooms, which is routinely done before consuming them raw or cooking them.

In addition, natamycin has a low toxicity profile, and information available on the metabolism of natamycin indicates that it is very poorly absorbed from the gastrointestinal tract. Furthermore, the pre-harvest interval (PHI) of four days should reduce available residues on mushrooms, as mushrooms grow rapidly during this period, allowing for a decreased level of active ingredient on the surface of the mushrooms at time of harvest.

Therefore, the use of Zivion M is not expected to result in unacceptable dietary risks when the product is used according to label instructions. In addition, as Zivion M is to be applied inside a closed growing house, exposure to natamycin in drinking water is not expected to occur.

3.2.2 Maximum Residue Limits (MRLs)

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine that the consumption of the maximum amount of residues that are expected to remain on food products when a pesticide is used according to label directions will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit under the *Pest Control Products Act* (PCPA) for the purposes of adulteration provision of the *Food and Drugs Act* (FDA). Health Canada sets science-based MRLs to ensure the food Canadians eat is safe.

Since the use of Zivion M at the maximum application rate as a fungicide on white button mushrooms is not expected to appreciably increase the dietary exposure to natamycin above the levels which are currently expected from its use as a food additive, the PMRA does not require the establishment of a maximum residue limit for natamycin.

3.3 Occupational and Bystander Risk Assessment

3.3.1 Use Description/Exposure Scenario

The commercial use for Zivion M is as a fungicide to suppress dry bubble disease on button mushrooms (*Agaricus bisporus*) in closed growing houses. The product is to be applied in the irrigation water by hose with an irrigating hand wand to the surface of the prepared mushroom bed as a surface drench, using appropriate dilution to ensure even coverage. Two applications may be applied, one at casing and one at pinning, at a rate of 2.0 mL Zivion M per square metre.

3.3.2 Mixer, Loader and Applicator Exposure and Risk Assessment

Occupational exposure to natamycin in Zivion M is expected to be mainly by the dermal route and may occur during mixing, loading or application activities. Personal protective equipment required for workers include a long sleeved shirt, long pants, shoes and socks, waterproof gloves and safety glasses. Other precautionary and hygiene statements on the label will require the user to avoid inhaling the spray mist, to wash hands thoroughly with soap and water after handling, and to remove contaminated clothing and wash clothing before reuse. Occupational exposure to Zivion M is therefore expected to be minimal when workers follow label instructions.

3.3.3 Bystander Exposure and Risk Assessment

Bystander exposure is expected to be negligible as the commercial application of Zivion M is expected to involve authorized personnel only, and enclosed mushroom growing houses are typically located where access to bystanders is limited.

3.3.4 Post-Application Exposure

Post-application activities include data gathering (for example, monitoring environmental conditions in mushroom growing houses, etc.) and harvesting. Exposure to workers performing post-application activities is expected to be minimal provided they follow label instructions which include personal protective equipment and hygiene statements. In addition, a pre-harvest interval of four days required on the label will further reduce worker exposure during harvesting of the mushrooms, as mushrooms grow rapidly during this period, allowing for a decreased level of active ingredient on the surface of the mushrooms at harvest.

3.4 Incident Reports Related to Human and Animal Health

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Health Canada website. No health-related incident reports for products containing natamycin have been received by PMRA. Incidents from the United States were searched and reviewed for products containing natamycin for use as pesticides. As of February 2, 2012, there were no health-related incident reports reported by the USEPA or the California Department of Pesticide Regulation (CalDPR) for end-use products containing this active ingredient.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

An initial screening of natamycin based on the physical-chemical properties suggests that natamycin is not likely to be a volatile compound. Dissociation constants (Iso-electric point at pH 6.5; pKa 8.35 and 4.6) suggest that natamycin could potentially be mobile at environmentally relevant pHs. An estimated log K_{ow} of -3.67 suggests that natamycin would not bioaccumulate in organisms. Natamycin is stable to hydrolysis at pH 5, 7, and 9, but will degrade rapidly when exposed to sunlight. Overall, the available information on the environmental fate of natamycin suggests that this compound is not volatile, stable to hydrolysis, and degrades rapidly in sunlight.

4.2 Environmental Risk Characterization

When the generation of quantitative data for non-conventional pest control products are not practical or apparent risks are considered minimal, a qualitative risk assessment, as was conducted for natamycin, is more appropriate.

As a part of mushroom production, a sterilization process is performed at the end of each production run, and as such, no residues of natamycin are expected to remain in the spent compost on disposal. Therefore, as potential environmental exposure should be negligible; there are no concerns for any non-target organisms that could be exposed to residues of natamycin from spent/reused mushroom compost medium.

Based on the use pattern for Zivion M, it was concluded that the use of natamycin in mushroom houses should not pose a risk to the environment. It should be noted, however, that the PMRA could require further data if natamycin is proposed for expansion to other uses, including greenhouse crops.

Incident Reports
No incidents are reported in the PMRA database or the USEPA Ecological Incident Information System (EIIS) for natamycin (or pimaricin).

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

Two trials conducted in mushroom houses were submitted for review. The casing surface was inoculated with *Verticillium fungicola* spores. Three rates, 0.6 mL, 1.0 mL, and 2.0 mL of Natamycin L (renamed Zivion M) per m^2 of mushroom bed, were tested against the commercial standard Bravo 500 Agricultural Fungicide. Natamycin L was applied twice (at casing and pinning) or four times (at casing, at pinning and between breaks). The number of mushrooms with spotting and/or bubbling symptoms was assessed. Yield and quality were assessed by determining the weight and number of marketable mushrooms.

Natamycin L treatment provided variable control of spots (18 – 65% control) and bubbles (48 - 94% control) compared to the inoculated untreated control. Bravo suppressed spots (63 - 78% control) and controlled bubbles (98% control). Application of Natamycin L at the higher rates was statistically comparable to the Bravo treatment. Treatment with Natamycin L significantly increased the weight (11 – 30% increase) and number (8 – 42% increase) of marketable mushrooms compared to the control. Yield increases for Bravo (34 – 38% increase in weight; 27 – 32% increase in counts) were comparable to the Natamycin L treatments in one trial, but were significantly higher in the other. Four applications of Natamycin L did not provide significantly higher levels of control of symptoms or greater increases in yield compared to two applications.

Reduction of dry bubble symptoms with Natamycin L was variable, although application at the higher proposed rate (2.0 mL/m^2) was comparable to the commercial standard. Although Bravo was more efficacious than Natamycin L against disease symptoms, yield increases indicate an economic benefit. Additional applications between breaks (total of four applications) did not increase the level of efficacy compared to applying at casing and pinning only (two applications). The tested low rate of 0.6 mL/m^2 did not consistently suppress disease symptoms; however, the higher rate of 2.0 mL/m^2 did demonstrate suppression. Based on the submitted efficacy data, the claim of suppression of dry bubble (*Verticillium fungicola*) on mushrooms is supported at 2.0 mL/m^2 of Zivion M with two applications; one at casing and one at pinning (Table 2, Appendix I).

5.2 Sustainability

5.2.1 Survey of Alternatives

Only two other fungicides with different modes of action (Group 1, Group M) are registered for control or suppression of dry bubble on mushrooms. Both fungicides (thiabendazole, chlorothalonil) have limitations in managing this disease on mushrooms. Group 1 fungicides are considered high risk for resistance development and *V. fungicola* has demonstrated resistance to thiabendazole in laboratory studies. Please refer to Table 3 (Appendix I) for additional information on registered products.

5.2.2 Compatibility with Current Management Practices Including Integrated Pest Management

Fungicides registered for dry bubble are applied at casing and pinning stages of production. Zivion M application occurs at the same timing. Rotating fungicides with different modes of action between production periods will help maintain sustainability of these products with respect to resistance management.

Inoculum is disseminated manually by workers, equipment or insect vectors. Insecticides registered for use in mushroom houses may be used during the production period. Sanitation of mushroom substrate and beds occurs prior to production and after harvest. The use of Zivion M to manage dry bubble can be integrated into mushroom production systems.

5.2.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Natamycin has been used in the food industry to control mould contamination and is not known to induce resistance in fungal pathogens. It also has no antibacterial activity, which suggests that there is no concern over development of resistance by human bacterial pathogens.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, natamycin and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Natamycin is not a concern with regard to the Track 1 criteria. It does not meet the bioaccumulation criterion (log $K_{ow} \geq 5$) with the log K_{ow} value of -3.67.

- Natamycin is not expected to be persistent or bioaccumulative in the environment.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade, Natamycin TGAI, and the end-use product, Zivion M, do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

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5 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, PMRA Formulants Policy.

7.0 Summary

7.1 Human Health and Safety

The available information for natamycin is adequate to qualitatively identify the toxicological hazards that may result from human exposure to natamycin. Natamycin TGAI is of low acute toxicity via the oral, dermal, and inhalation routes. It is severely irritating to the eyes, slightly irritating to the skin, is not a dermal sensitizer, and is considered to be non-mutagenic. Zivion M is non to minimally irritating to the eyes.

Occupational exposure to Zivion M is expected to be minimal if the precautionary statements and recommended personal protective equipment on the product label, which are intended to minimize worker exposure, are observed. Bystander exposure is likely to be negligible. Post-application exposure can be minimized by following the precautionary statements on the label, and by observing the pre-harvest interval.

Dietary exposure to natamycin from the use of Zivion M is not expected to result in unacceptable dietary risks when the product is used according to label instructions. A maximum residue limit is not required for natamycin.

7.2 Environmental Risk

Natamycin is a substance that is naturally occurring in the environment. The exposure of non-target organisms to natamycin via Zivion M under operational conditions is considered to be negligible and, as such, risks to the environment will be negligible for the proposed use.

7.3 Value

The efficacy data submitted to register Zivion M was sufficient to support the claim of suppression of dry bubble (*Verticillium fungicola*) on mushrooms. Registration of this product will provide another tool to mushroom growers in managing this disease. Zivion M does not negatively affect mushroom yield and will contribute to resistance management of currently registered fungicides.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Natamycin TGAI and Zivion M containing the technical grade active ingredient natamycin to suppress dry bubble disease in mushroom production.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
a.i.	active ingredient
atm	atmosphere
bw	body weight
°C	degree(s) Celcius
CalDPR	California Department of Pesticide Regulation
CAS	Chemical Abstracts Service
cm	centimetres
EFSA	European Food Safety Authority
EIIS	Ecological Incident Information System
FAO	Food and Agriculture Organization
FDA	Food and Drugs Act
g	gram
ha	hectare(s)
Hg	mercury
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	kilogram
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
K_{ow}	*n*–octanol-water partition coefficient
LOAEL	lowest observed adverse effect level
m^2	metre(s) squared
m^3	metre(s) cubed
mg	milligram
MIS	maximum irritation score
MIIS	maximum individual irritation score
mL	millilitre
MRL	maximum residue limit
NOAEL	no observed adverse effect level
Pa	Pascal(s)
PCPA	Pest Control Products Act
PHI	pre-harvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WHO	World Health Organization
wt	weight

Appendix I Tables and Figures

Table 1 Summary of acute toxicity, irritative effects, sensitization and mutagenicity information for natamycin

Study	Species/Strain And Doses	Result	Target Organ / Significant Effects / Comments	Reference
Oral toxicity (Limit test) Exposure by gavage	Rat – Sprague Dawley (5 females)	LD_{50} (♀) > 2000 mg/kg bw **Low acute toxicity.**	One mortality occurred.	1907352
Dermal	Rat – Sprague Dawley (5/sex)	LD_{50} (♀) > 5050 mg/kg bw LD_{50} (♂) > 5050 mg/kg bw **Low acute toxicity.**	No mortality occurred.	1907354
Inhalation Nose-only exposure chamber	Rat – Sprague Dawley (5/sex)	LC_{50} (♀) > 2.39 mg/L LC_{50} (♂) > 2.39 mg/L **Low acute toxicity.**	No mortality occurred.	1907355
Eye Irritation Draize method	Rabbit – New Zealand White (3 males) Dose: 0.1 mL of test substance. Eyes were left unwashed.	MIS[a] = 62/110 (at 1 hour) **Severely irritating.**	Iritis and corneal opacity cleared by 24 hours, and conjunctivitis cleared in all animals by 48 hours.	1907356
Dermal Irritation Draize method	Rabbit – New Zealand White (3 males) Dose: 500 mg of test substance moistened with 0.5 mL water applied for 4 hours.	MIIS[b] = 1/8. **Slightly irritating.**	Slight erythema cleared by 24 hours.	1907357
Dermal Sensitization Local Lymph Node Assay	Mice – CBA/J Test group = 15 Naïve control group = 5 Positive control group = 5	Negative results. Not a dermal sensitizer.	No positive reactions were observed following challenge in any test or negative control animals.	1907358
Bacterial reverse mutation assay Plate incorporation test	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and *Escherichia coli* strain WP2uvrA Test concentrations: 0, 33, 100, 333, 1000, and 3330 µg/plate, with and without metabolic activation.	Non-mutagenic.	No biologically relevant increases in revertant colony numbers of any of the tester strains were observed at any concentration, in the presence or absence of metabolic activation.	1907361

Study	Species/Strain And Doses	Result	Target Organ / Significant Effects / Comments	Reference
In vitro mammalian chromosomal aberration assay	Human lymphocytes in culture Test concentrations: 0, 1, 3, and 10 µg/mL, with and without metabolic activation.	Non-mutagenic.	No evidence of treatment-induced mutagenicity or effects on mitotic index were observed.	1907363

[a]MIS: Maximum mean irritation score
[b]MIIS: Maximum individual irritation score

Table 2 Use (label) Claims Proposed by Applicant and Acceptability

Applicant proposed label claim	PMRA supported label claim
Control of dry bubble (*Verticillium fungicola*) on mushrooms with Natamycin L applied 0.6 – 2.0 mL/m^2. Apply Natamycin L diluted in 2.5 L water at casing and at pinning. Apply Natamycin L diluted in 1.25 L water between breaks. (Maximum 4 applications)	Supported as suppression of dry bubble at 2.0 mL/m^2 diluted in sufficient water to ensure an even application applied at casing and at pinning (maximum 2 applications).

Table 3 Registered Alternative Fungicides to Manage Dry Bubble (*Verticillium fungicola*) on Mushrooms

Product (active Ingredient)	Mode of Action Group	Level of Control	Application Timing
Mertect SC Fungicide (thiabendazole)	1	Suppression	One application at casing.
Bravo 500 Agricultural Fungicide, Bravo Ultrex 90 SDG Agricultural Fungicide (chlorothalonil)	M	Control	One application at casing and a second application at pinning.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA #	Documentation
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1907343	2010, Specifications Non CBI, DACO: 2.12
1907344	2010, Specifications CBI, DACO: 2.12, 2.12.1 **CBI**
1907345	2010, Preliminary Analysis CBI, DACO: 2.13 **CBI**
1907346	2010, Preliminary Analysis Non CBI, DACO: 2.13, 2.13.1, 2.13.2, 2.13.3
1907347	2010, Chemical and Physical Properties, DACO: 2.14, 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.14, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9
1907348	2010, Stability, DACO: 2.14.13 **CBI.**
1907396	2010, **CBI reference document** - Product Identification, Formulants, Formulation Process and Certified Limits CBI, DACO: 3.2.2,3.2.3,3.3.1 **CBI**
1907399	2010, Natamycin L Enforcement Analytical Method, DACO: 3.4.1.
1907401	J.A.B. van der Lee, 2010, Natamycin L Chemical and Physical Properties, DACO:3.5,3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3,3.5.4,3.5.5,3.5.6,3.5.7,3.5.8,3.5.9.
1907402	2010, Natamycin L Storage Stability and Corrosion Characteristics, DACO: 3.5.10, 3.5.14.
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2003919	2011, Spec Sheet Foam Control 30, DACO: 3.2.2 **CBI**
2020626	2011, 12-Month Stability Study Report on Natamycin L, DACO: 3.5.10, 3.5.14 **CBI.**
2077272	2011, 18- Month Storage Stability and Corrosion Characteristics, DACO: 3.5.10, 3.5.14 **CBI.**
2136240	2011, External Standard Retention Time behaviour - email, DACO: 3.5.10 **CBI.**

2.0 Human and Animal Health

PMRA #	Documentation
1907352	Acute Oral Toxicity Study – Natamycin TGAI, DACO 4.2.1.
1907354	Acute Dermal Toxicity Study – Natamycin TGAI, DACO 4.2.2.
1907355	Acute Inhalation Toxicity Study – Natamycin TGAI, DACO 4.2.3.
1907356	Primary Eye Irritation Study – Natamycin TGAI, DACO 4.2.4.
1907357	Primary Dermal Irritation Study – Natamycin TGAI, DACO 4.2.5.
1907358	Dermal Sensitization Study – Natamycin TGAI, DACO 4.2.6.
1907359	Short-term Oral Toxicity – Natamycin TGAI, DACO 4.3.1.
1922406	Prenatal Developmental Toxicity – Natamycin TGAI, DACO 4.5.2.
2110525	Waiver to address Prenatal Developmental Toxicity – Natamycin TGAI, DACO 4.5.2.
1907361	Bacterial Reverse Mutation Assay – Natamycin TGAI, DACO 4.5.4.
1907363	In vitro Mammalian Chromosomal Aberration Assay – Natamycin TGAI, DACO 4.5.5.
1907405	Marin J.E., 2009. Magnitude of the residue of natamycin in mushrooms. DACO 7.4.1.
1907414	Use Description/Scenario for Natamycin L, DACO 5.2.
1922403	Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2001. Safety Evaluation of Certain Food Additives and Contaminants. Natamycin (Pimaricin). WHO Food Additives Series: 48.
2110525	EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS); Scientific Opinion on the use of natamycin (E235) as a food additive. EFSA Journal 2009; 7(12):1412.
1907412	2010, Request for Waiver of 5 Acute Toxicity Tests CBI, DACO: 4.6.1,4.6.2,4.6.3,4.6.4,4.6.5,4.6.6 CBI
1907413	2009, Acute Eye Irritation Study in Rabbits, DACO: 4.6.4

1907403 2010, Development and Validation of an Analytical Method for the Determination of Natamycin in Mushrooms and Mushroom Compost, Casing and Casing Plus Inoculum, DACO: 7.2.1

3.0 Environment

1922391 2010, Request for Waiver of Data Requirements, DACO: 9.2.4.1,9.2.4.2,9.2.5,9.2.6,9.2.7

1907366 2010, Tier III Summary, DACO: 12.7

4.0 Value

PMRA # Documentation

1907415 2010, Natamycin L Value Summary, DACO: 10.1,10.2.1,10.2.2,10.2.3.1

1907416 2009, Influence of Natamycin L on Mushroom Production, DACO: 10.2.3.3

1907418 2009, Screening of Delvocid Liquid 05096 against *Verticillium fungicola*, DACO: 10.2.3.3

1922393 2010, DACO 10.3.1 Adverse Effects on Use Site Summaries, DACO: M10.3.1

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

Joint FAO/WHO Expert Committee on Food Additives (JECFA), Sixty-Seventh Meeting. Rome, Italy, 20-29 June 2006. Summary and Conclusions, issued 7 July 2006.

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